REMARKS/ARGUMENTS

In the Claims, please cancel Claims 9 through 11 without prejudice. Claims 1, 3, 13 and 15 have been amended in response to the Examiner's rejections and to correct minor typographical errors. New Claim 17 has been added. These changes to the pending claims and the addition of New Claim 17 are fully supported by the Application as originally filed on page 2, lines 14-16 and page 6, lines 7-9. No new matter has been added.

Rejection Under 35 U.S.C. § 102

Claims 1, 4, 9-11, and 13-16 are rejected under 35 U.S.C. § 102(e), as being anticipated by US Patent No. 6,551,617 to Corbo et al. ("Corbo").

According to the Manual of Patent Examining Procedure ("MPEP") Section 2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 6187, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Corbo does not anticipate any of the Claims of the present invention as set forth herein.

Corbo discloses a "coating composition" (col. 5, lns. 4-9) that is used to coat granules or crystals of drug ingredient in a fluid bed coater (col. 5, lns. 48-49). The Examiner states that Corbo teaches the formulation of Claims 1, 4 and 10 by its mention of the optional use of ethyl cellulose as an additive in an amount of approximately 10-30 weight percent of the coating composition (Col. 4, lines 55-65). Not only does Corbo fail to disclose the particular cellulosic polymers claimed by the Applicant, it fails to teach the weight percent of cellulose polymer in the total formulation rather than just the coating.

Applicant's invention is directed to a sustained/prolonged release pharmaceutical formulation that has a water-soluble medicament uniformly associated with a polymer construct, wherein the formulation

exhibits unique sustained-release properties based on the nature of the polymer construct. The polymer construct is comprised of a mixture of polyvinylacetate ("PVA") and polyvinylpyrrolidone ("PVP"), and one or more cellulose ether polymers that have hydroxyethyl, hydroxypropyl or hydroxypropyl methyl substitution. The cellulosic polymers make up approximately 2 to 60 weight percent of the total formulation.

Applicant's claims have been amended to this affect:

Claims 1 and 13 have been amended to specify that the water-soluble medicament is blended with a polymer construct, wherein the cellulose ether polymer is a mixture of at least one cellulose ether polymer wherein the cellulose ether polymer comprises from about 2 to about 60 weight percent of the total formulation.

Claim 3 has been amended and New Claim 17 has been added to specify that the at least one cellulose ether polymer has hydroxyethyl-, hydroxypropyl-, or hydroxypropyl methyl- substitution.

As a result, the Applicant respectfully submits that Corbo fails to disclose all of the limitations of the claims of the present invention and that the claim amendments have rendered the Examiner's rejection under 35 U.S.C. 102(e) moot.

Rejection Under 35 U.S.C. § 103

Claim 3 is rejected under 35 U.S.C. § 103 as obvious over US Patent No. 6,551,617 to Corbo et al. ("Corbo").

One of the three basic requirements to establish a *prima facie* case of obviousness is the requirement for some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See* MPEP § 2143. The Examiner states that it would have been obvious to one of ordinary

skill in the art to use any of the commercially available cellulose ether polymers listed by the Applicant in the coating composition of Corbo, relying on the knowledge of persons or ordinary skill in the art to provide a source of motivation to modify the reference. *See* MPEP § 2143.01.

The modification proposed by the Examiner, substitution of hydroxyethyl-, hydroxypropyl-, or hydroxypropyl methyl- substituted cellulose polymers for the ethyl cellulose disclosed in Corbo, would render Corbo's coating composition unsatisfactory for its intended purpose – taste masking. When determining whether a *prima facie* case of obviousness has been established, the proposed modification cannot render the prior art unsatisfactory for its intended purpose. *See* MPEP § 2143.01 (citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)).

Corbo requires a "coating composition that is insoluble in the mouth", or insoluble at a pH of about 7 (col. 2, lns. 46-50; col. 7, Tables 3 and 4). Ethyl cellulose is not water-soluble. *See* Ainley Wade and Paul J. Weller, *Handbook of Pharmaceutical Excipients*, 186-187 (2d ed. 1994) ("Handbook"). Further, ethyl cellulose is primarily used as a hydrophobic coating agent in pharmaceutical formulations. When used in tablet formations, the tablets tend to demonstrate poor dissolution. *See* Handbook, at 186.

As stated above, the Applicant's claims have been amended to specify the cellulose ether polymers required by the present invention, namely, the amendment of Claim 3 and the addition of New Claim 17 to specify that the at least one cellulose ether polymer has hydroxyethyl-, hydroxypropyl-, or hydroxypropyl methyl- substitution.

All of the cellulosic polymers claimed by Applicant, namely, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose are water-soluble and are known in the art for their use in pharmaceutical formulations as binders and extended-release tablet matrices. *See* Handbook, at 219-220, 223-224, and 229-230, respectively.

As a result, the Applicant respectfully disagrees that the present invention is obvious over Corbo. If one of ordinary skill in the art were to substitute a water-soluble cellulose polymer, i.e. hydroxyethyl cellulose, hydroxypropyl cellulose, or hydroxypropyl methylcellulose, for ethyl cellulose as it is intended to be used in Corbo, the resulting coated composition would dissolve rapidly in the mouth, and on the way down to the stomach, completely eliminating the effectiveness of the coating and unveiling the undesirable taste of the medicament. As a result, Applicant respectfully submits that one of ordinary skill in the art would not be motivated to make the substitution, that Corbo teaches away from using water-soluble components in the coating composition, and therefore Corbo does not render any of the claims of the present invention obvious.

Based on the amendments and remarks set forth above, the Applicant hereby respectfully requests that the Examiner's objections and rejections be withdrawn and that the Application is in condition for allowance. Should the Examiner have questions or require additional information or clarification, please do not hesitate to contact the Applicant's undersigned attorney. Please charge any required fees to our Deposit Account No. 50-2543.

Respectfully submitted,

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4/3

Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by
Ainley Wade and **Paul J Weller**

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Ethylcellulose

1. Nonproprietary Names

BP: Ethylcellulose
PhEur: Ethylcellulosum
USPNF: Ethylcellulose

2. Synonyms

Aquacoat; E462; *Ethocel*; *Surelease*.

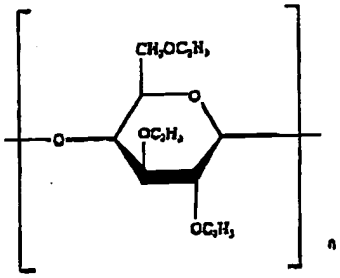
3. Chemical Names and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

4. Empirical Formula Molecular Weight

Ethylcellulose is an ethyl ether of cellulose, a long-chain polymer consisting of anhydroglucose units joined together by acetal linkages. Each anhydroglucose unit has three replaceable hydroxyl groups which are substituted to the extent of 2.25–2.60 ethoxyl groups (OC_2H_5) per unit, equivalent to an ethoxyl content of 44–51%.

5. Structural Formula



Structure shown with complete ethoxyl substitution. *See also* Section 4.

6. Functional Category

Coating agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations.

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.[1-5] Ethylcellulose coatings are used to modify the release of a drug,[5] to mask an unpleasant taste, or to improve the stability of a formulation, e.g. ethylcellulose dissolved in propan-2-ol is used to coat ascorbic acid granules to prevent oxidation. Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.[6]

Ethylcellulose, dissolved in an organic solvent, or solvent mixture, can be used on its own to produce water-insoluble films. Higher viscosity ethylcellulose grades tend to produce stronger, tougher films. Ethylcellulose films may be modified, to alter their solubility, by the addition of hydroxypropylmethylcellulose[7] or a plasticizer, *see* Section 19. An aqueous polymer dispersion (or latex) of ethylcellulose such as *Aquacoat* (FMC Corporation) may also be used to produce ethylcellulose films without the need for organic solvents. W coats of hydrated ethylcellulose, drug release is via diffus This can be a slow process unless a large surface area is utili and aqueous ethylcellulose dispersions tend therefore to used to coat granules.[8,9]

Ethylcellulose is also widely used in drug microencapsu tion,[10-14] high viscosity grades usually being used. Release a drug from an ethylcellulose microcapsule is a function of microcapsule wall thickness.[12]

In tablet formulations, ethylcellulose may additionally employed as a binder, the ethylcellulose being blended dry wet-granulated with a solvent such as ethanol (95% Ethylcellulose produces hard tablets, with low friability; th may however demonstrate poor dissolution.

In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions or gels, provided an appropriate solvent is used.

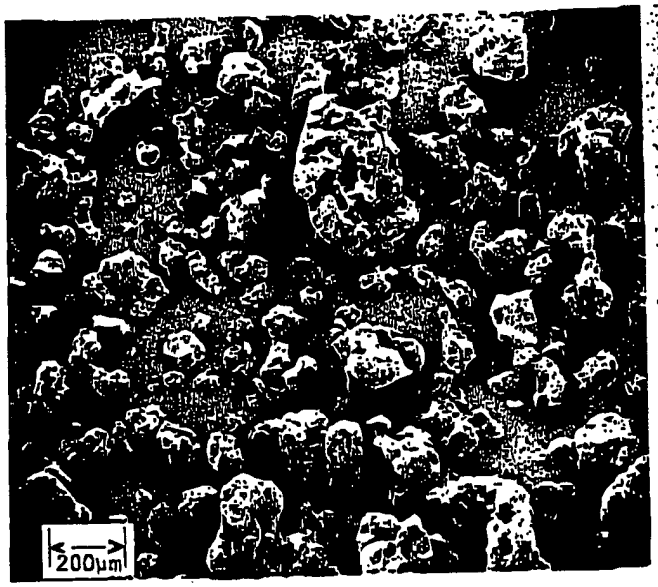
Ethylcellulose is additionally used in cosmetics and food products.

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained release tablet coating	3.0–10.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

8. Description

Ethylcellulose is a tasteless, free-flowing, white to light tan colored powder.

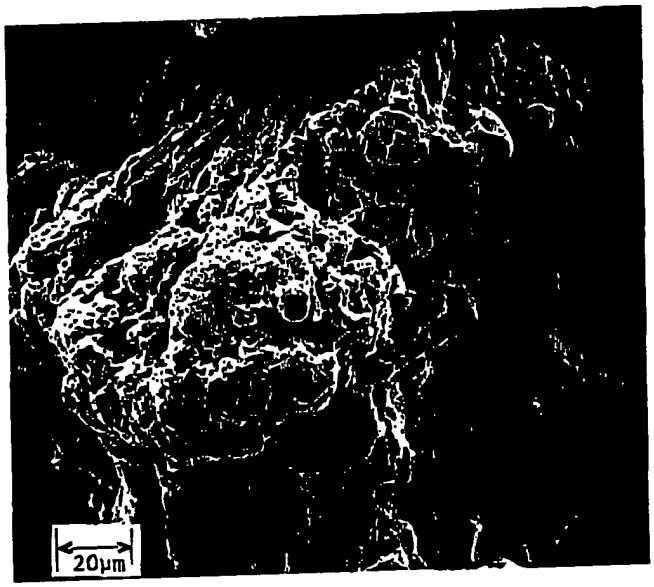
SEM: 1
Excipient: Ethylcellulose
Manufacturer: Hercules Ltd
Lot No.: 57911
Magnification: 60x
Voltage: 10 kV



SEM: 2
Excipient: Ethylcellulose
Manufacturer: Hercules Ltd
Lot No.: 57911
Magnification: 600x
Voltage: 10 kV

SEM: 3
Excipient: Ethylcellulose (*Ethocel*)
Manufacturer: Dow Chemical Company
Lot No.: 103051
Magnification: 60x
Voltage: 10 kV

SEM: 4
Excipient: Ethylcellulose (*Ethocel*)
Manufacturer: Dow Chemical Company
Lot No.: 103051
Magnification: 600x
Voltage: 10 kV



9. Pharmacopeial Specifications

Test	PhEur 1993	USPNF XVII
Identification	+	+
pH (2% w/w suspension)	5.0-7.5	—
Viscosity	+	+
Loss on drying	⩽ 3.0%	⩽ 3.0%
Residue on ignition	—	⩽ 0.4%
Sulfated ash	⩽ 0.5%	—
Arsenic	—	⩽ 3 ppm
Lead	—	⩽ 10 ppm
Heavy metals	⩽ 20 ppm	⩽ 40 ppm
Acetaldehyde	⩽ 100 ppm	—
Chlorides	⩽ 0.05%	—
Assay (of ethoxyl groups)	—	44.0-51.0%

10. Typical Properties

Density (bulk): 0.4 g/cm^3
Glass transition temperature: 130-133°C[3]
Hygroscopicity: ethylcellulose absorbs very little water at high relative humidities or during immersion; any absorbed water evaporates readily.[15] *See also* HPE Data.
Solubility: practically insoluble in glycerin, propylene glycol and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol and toluene.
Specific gravity: 1.12-1.15
Viscosity: various grades of ethylcellulose are commercially available which differ in their ethoxyl content and degree of polymerization. They may be used to produce 5% w/v

Ethylcellulose

solutions, in organic solvents, with viscosities of 6-110 mPa s (6-110 cP), *see also* Section 19. Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce stronger, tougher films. The viscosity of solutions increases with an increase in concentration of ethylcellulose, e.g. the viscosity at 25°C of a 5% w/v solution of *Ethocel* in an 80/20 toluene/ethanol solvent blend is 4 mPa s (4 cP), whilst a 25% w/v solution in the same solvent mixture has a viscosity of 850 mPa s (850 cP). Solutions with a lower viscosity may be obtained by incorporating a higher percentage (up to 35%) of a low molecular weight aliphatic alcohol, such as methanol or ethanol, in a solvent mixture. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of the other aromatic solvent.

	HPE Laboratory Project Data		
	Method	Lab #	Results
Average flow rate	FLO-3	24	1.66 g/s [b]
Moisture content	MC-29	23	1.853% [a]
	MC-20	15	0.700% [a]
	MC-29	23	1.020% [b]
	EMC-1	15	*See* Fig. 1. [a]
Particle friability	PF-1	36	0.068% [b]
Particle size	PSD-6	23	*See* Fig. 2. [a]
	PSD-6	23	*See* Fig. 3. [b]
Solubility	SOL-6	23	
Ethanol (95%) at 25°C			53 mg/mL [a]
Ethanol (95%) at 25°C			15 mg/mL [b]
Ethanol (95%) at 37°C			66 mg/mL [a]
Ethanol (95%) at 37°C			25 mg/mL [b]
Hexane at 25°C			< 2 mg/mL [a]
Hexane at 25°C			< 2 mg/mL [b]
Hexane at 37°C			< 6 mg/mL [a]
Hexane at 37°C			< 6 mg/mL [b]
Propylene glycol at 25°C			25 mg/mL [a]
Propylene glycol at 25°C			25 mg/mL [b]
Propylene glycol at 37°C			25 mg/mL [a]
Propylene glycol at 37°C			25 mg/mL [b]
Water at 25°C			< 1 mg/mL [a]
Water at 25°C			10 mg/mL [b]
Water at 37°C			< 1 mg/mL [a]
Water at 37°C			10 mg/mL [b]

Supplier: a. Hercules Ltd (Lot No.: 58587); b. Dow Chemical Company.

11. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than cellulose esters.

Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of an antioxidant and a compound with light absorption properties between 230-340 nm.

The bulk material should be stored in a dry place, in a well-closed container at a temperature between 7-32°C.

12. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

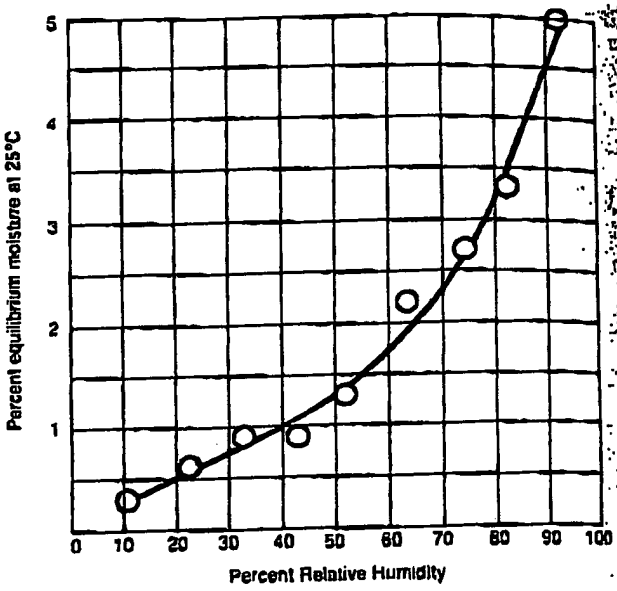


Fig. 1: Equilibrium moisture content of ethylcellulose.[15]

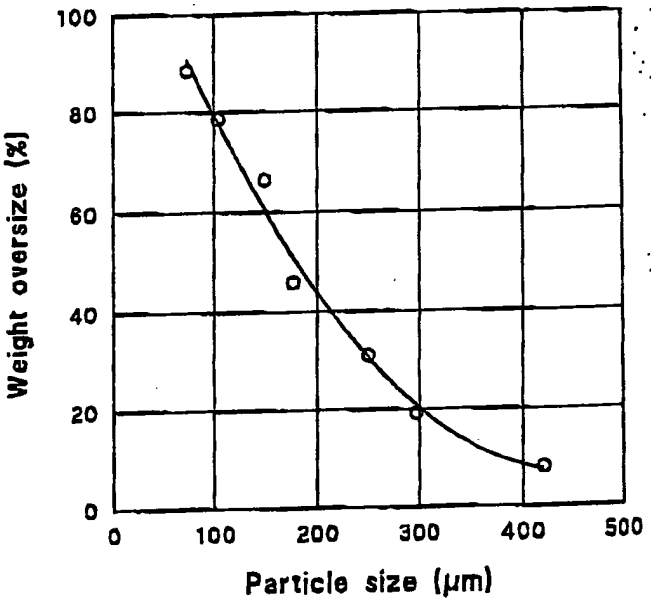


Fig. 2: Particle size distribution of ethylcellulose.

13. Method of Manufacture

Ethylcellulose is prepared from wood pulp by treatment with alkali followed by ethylation of the alkali cellulose with chloroethane.

14. Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products.

Ethylcellulose is not metabolized following oral consumption and is therefore a noncaloric substance. It is generally regarded as a nontoxic, nonallergenic and nonirritant material. Since ethylcellulose is not metabolized it is not recommended for use in parenteral products; parenteral use may be harmful to the kidneys.

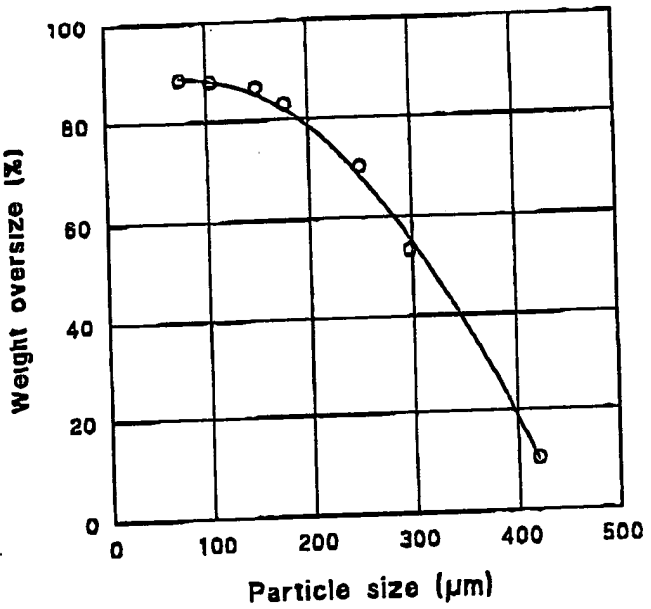


Fig. 3: Particle size distribution of ethylcellulose (*Ethocel*).

The WHO has not specified an acceptable daily intake of ethylcellulose since the level of use in foods was not considered to be a hazard to health.[16]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dust may be irritant to the eyes and eye protection should therefore be worn. Excessive dust generation should be avoided to minimize the risk of explosions. Ethylcellulose is combustible.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions and tablets, topical emulsions and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Eur, Mex and USPNF.

18. Related Substances

Methylcellulose.

19. Comments

Ethylcellulose is compatible with the following plasticizers: dibutyl phthalate; diethyl phthalate; dimethyl phthalate; benzyl benzoate; butyl and glycol esters of fatty acids; refined mineral oils; oleic acid; stearic acid; cetyl alcohol; stearyl alcohol; castor oil; corn oil; camphor and numerous other materials.

Various grades of ethylcellulose are commercially available which differ in their ethoxyl content and physical properties, see Table I.

Table I: Comparison of different grades of ethylcellulose.

Grade	Viscosity (mPa s)*	Mean particle diameter (μm)
Aqualon N7	5.3	160 (a)
Aqualon N10	5.5	225 (a)
Aqualon N100	80.0	194 (a)
Ethocel Std 4	5.4	204 (b)
Ethocel Std 7	6.4	210 (b)
Ethocel Std 10	10.6	212 (b)
Ethocel Std 20	19.3	243 (b)
Ethocel Std 45	47.6	305 (b)
Ethocel Std 100	95.9	280 (b)
Ethocel Med 50	55.0	262 (b)
Ethocel Med 70	66.9	280 (b)
Ethocel Med 100	98.6	286 (b)

* Viscosities are for a 5% w/v solution at 25°C. Solvent is the supplier's recommended blend of toluene/ethanol.
Supplier: a. Aqualon Company; b. Dow Chemical Company.

20. Specific References

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15. Callahan JC, Cleary GW, Elefant M, Kaplan G, Kensler T, Nash RA. Equilibrium moisture content of pharmaceutical excipients. Drug Dev Ind Pharm 1982; 8: 355-369.
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Rowe RC. Molecular weight studies on ethyl cellulose used in film coating. Acta Pharm Suec 1982; 19: 157-160.
Rowe RC. Materials used in the film coating of oral dosage forms. In: Florence AT, editor. Critical reports on applied chemistry, volume 6: materials used in pharmaceutical formulation. Oxford: Blackwell Scientific Publications, 1984: 1-36.

22. Authors

USA: TC Dahl.

Hydroxyethyl Cellulose

Nonproprietary Names

BP: Hydroxyethylcellulose
PhEur: Hydroxyethylcellulosum
USPNF: Hydroxyethyl cellulose

Synonyms

Celloramnosan; *Celloxize*; cellulose, hydroxyethyl ether; HEC; *Hydroramnosan*; *Liporamnosan*; *Natrosol*.

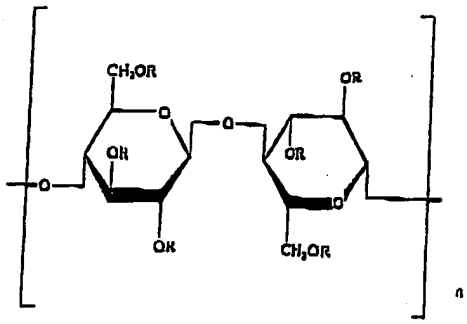
Chemical Name and CAS Registry Number

Cellulose, 2-hydroxyethyl ether [9004-62-0]

Empirical Formula Molecular Weight

The USPNF XVII describes hydroxyethyl cellulose as a partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades, varying in viscosity and degree of substitution, and some grades are modified to improve their dispersion in water. The grades are distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/v solution measured at 20°C. Hydroxyethyl cellulose may also contain a suitable anticaking agent.
See Section 5.

Structural Formula



where R is H or $[-CH_2CH_2O-]_mH$

Functional Category

Binding agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hydroxyethyl cellulose is a nonionic, water soluble polymer commonly used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic[1] and topical formulations[2] although it is also used as a binder[3] and coating agent for tablets.[4]

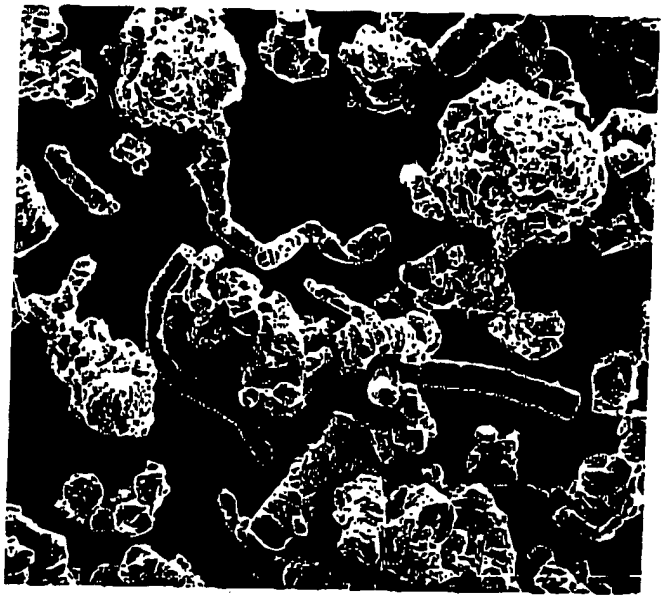
The concentration of hydroxyethyl cellulose used in a formulation is dependent upon the solvent and the molecular weight of the grade.

Hydroxyethyl cellulose is also widely used in cosmetics.

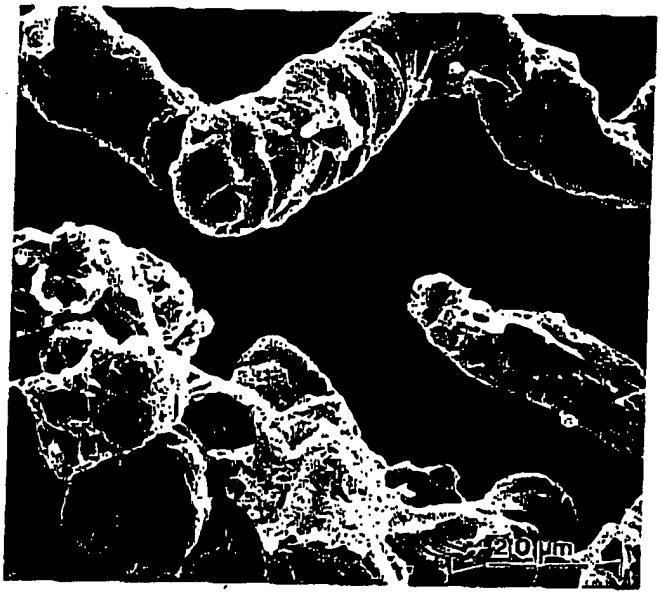
8. Description

Hydroxyethyl cellulose occurs as a light tan or cream to white-colored, odorless and tasteless, hygroscopic powder.
See Sections 4 and 5.

SEM: 1
Excipient: Hydroxyethyl cellulose (*Natrosol*)
Manufacturer: Aqualon
Magnification: 120x



SEM: 2
Excipient: Hydroxyethyl cellulose (*Natrosol*)
Manufacturer: Aqualon
Magnification: 600x



9. Pharmacopeial Specifications

Test	PhEur 1984	USPNF XVII (Suppl 6)
Identification	+	+
Appearance of solution	+	—
Viscosity	+	+
pH (1 in 100)	5.5-8.5	6-8.5
Loss on drying	≤ 10.0%	≤ 10.0%
Lead	—	≤ 0.001%
Residue on ignition	—	≤ 5.0%
Sulfated ash	≤ 4.0%	—
Arsenic	—	≤ 3ppm
Chlorides	≤ 1.0%	—
Heavy metals	≤ 20 ppm	≤ 0.004%
Organic volatile impurities	—	+
Nitrates	+	—

10. Typical Properties

Acidity/alkalinity: pH = 5.5-8.5 for a 1% w/v aqueous solution.

Ash:
2.5% w/w for *Cellosize*;
3.5% w/w for *Natrosol*.

Autoignition temperature: 420°C

Density (bulk):
0.35-0.61 g/cm^3 for *Cellosize*;
0.60 g/cm^3 for *Natrosol*.

Melting point: softens at 135-140°C, decomposes at about 205°C.

Moisture content: commercially available grades of hydroxyethyl cellulose contain less than 5% w/w of water. However, hydroxyethyl cellulose is hygroscopic, the amount of water absorbed depending upon the initial moisture content and the relative humidity of the surrounding air. Typical equilibrium moisture values for *Natrosol 250* at 25°C are: 6% w/w at 50% relative humidity and 29% w/w at 84% relative humidity.

Particle size distribution: for *Cellosize*, 100% through a US #80 mesh (177 μm); for *Natrosol* (regular grind), 10% retained on a US #40 mesh (420 μm); for *Natrosol* (X-grind) 0.5% retained on a US #60 mesh (250 μm).

Refractive index:
n_D^{20} = 1.336 for a 2% w/v aqueous solution.

Solubility: hydroxyethyl cellulose is soluble in either hot or cold water, forming clear, smooth, uniform solutions. Practically insoluble in acetone, ethanol, ether, toluene and most other organic solvents. In some polar organic solvents, such as the glycols, hydroxyethyl cellulose either swells or is partially soluble.

Specific gravity: 1.38-1.40 for *Cellosize*; 1.0033 for a 2% w/v aqueous hydroxyethyl cellulose solution.

Surface tension: *see* Table I.

Table I: Surface tension (mN/m) of different *Cellosize* (Amerchol Corp) grades at 25°C.

Concentration of aqueous solution (% w/v)	WP-02	*Cellosize* grade 09	300	QP4400	52000	100M
0.01	65.8	65.7	66.4	66.3	65.9	66.1
0.1	65.3	65.4	65.8	65.3	65.4	65.4
1.0	64.4	65.1	65.5	65.8	66.1	66.3

Table I: *Continued*

Concentration of aqueous solution (% w/v)	WP-02	*Cellosize* grade 09	300	QP4400	52000	100M
2.0	64.2	65.0	66.3	67.3	—	—
5.0	64.1	64.7	—	—	—	—
10.0	64.4	65.9	—	—	—	—

Viscosity (dynamic): hydroxyethyl cellulose is available in a wide range of viscosity types, e.g. *Cellosize* is manufactured in eleven regular viscosity grades. Hydroxyethyl cellulose grades differ principally in their aqueous solution viscosities which range from 2-20000 mPa s for a 2% w/v aqueous solution. Two types of *Cellosize* are produced, a WP-type, which is a normal-dissolving material, and a QP-type, which is a rapid-dispersing material. The lowest viscosity grade (02) is available only in the WP-type. Five viscosity grades (09, 3, 40, 300 and 4400) are produced in both WP- and QP-types. Five high-viscosity grades (10000, 15000, 30000, 52000, and 100M) are produced only in the QP-type. Table II shows the standard *Cellosize* grades and types available and their respective viscosity ranges in aqueous solution.

Natrosol 250 has a degree of substitution of 2.5 and is produced in ten viscosity types. The suffix 'R' denotes that *Natrosol* has been surface treated with glyoxal to aid in solution preparation, *see* Table III.

Aqueous solutions made using a rapidly dispersing material may be prepared by dispersing the hydroxyethyl cellulose in mildly agitated water at 20-25°C. When the hydroxyethyl cellulose has been thoroughly wetted the temperature of the solution may be increased to 60-70°C to increase the rate of dispersion. Making the solution slightly alkaline also increases the dispersion process. Typically, complete dispersion may be achieved in approximately an hour by controlling the temperature, pH and rate of stirring.

Normally dispersing grades of hydroxyethyl cellulose require more careful handling to avoid agglomeration during dispersion; the water should be vigorously stirred. Alternatively, a slurry of hydroxyethyl cellulose may be prepared in a nonaqueous solvent, such as ethanol, prior to dispersion in water.

See also Section 11 for information on solution stability.

Table II: Approximate viscosities of various grades of aqueous *Cellosize* (Amerchol Corp) solutions at 25°C.

Type	Grade	Concentration (% w/v)	Viscosity (mPa s)* Low	High
WP	02	5	7-14	14-20
WP &	09	5	60-100	100-140
QP	3	5	220-285	285-350
	40	2	70-110	110-150
	300	2	250-325	325-400
	4400	2	4200-4700	4700-5200
QP	10000	2	5700	6500
	15000	2	15000-18000	18000-21000
	30000	1	950-1230	1230-1500
	52000	1	1500-1800	1800-2100
	100M	1	2500	3000

* *Cellosize* viscosity grades are available in narrower ranges, as noted by the Low and High designation.

Table III: Approximate viscosities of various grades of aqueous *Natrosol 250* (Aqualon) solutions at 25°C.

Type	Viscosity (mPa s) for varying concentrations (% w/v). 1%	2%	5%
HHR	3400-5000	—	—
H4R	2600-3300	—	—
HR	1500-2500	—	—
MHR	800-1500	—	—
MR	—	4500-6500	—
KR	—	1500-2500	—
GR	—	150-400	—
ER	—	25-105	—
JR	—	—	150-400
LR	—	—	75-150

	HPE Laboratory Project Data Method	Lab#	Results
Particle Friability			
Natrosol 250L	PF-1	36	0.050%
Natrosol 250HHR	PF-1	36	0.008%
Viscosity			
Natrosol 250L (5%)	VIS-4	6	150-225 mPa s
Natrosol 250MR (1%)	VIS-4	6	190-375 mPa s
Natrosol 250MR (2%)	VIS-4	6	4250-7250 mPa s
Natrosol 250HHR (1%)	VIS-4	6	3275-5875 mPa s

Supplier: Aqualon.

11. Stability and Storage Conditions

Hydroxyethyl cellulose powder is a stable, though hygroscopic, material.

Aqueous solutions of hydroxyethyl cellulose are relatively stable between pH 2-12 with the viscosity of solutions being largely unaffected. However, solutions are less stable below pH 5 due to hydrolysis. At high pH, oxidation may occur.

Increasing temperature reduces the viscosity of aqueous hydroxyethyl cellulose solutions. However, on cooling, the original viscosity is restored. Solutions may be subjected to freeze-thawing, high temperature storage or boiling without precipitation or gelation occurring.

Hydroxyethyl cellulose is subject to enzymatic degradation, with consequent loss in viscosity of its solutions.[5] Enzymes which catalyze this degradation are produced by many bacteria and fungi present in the environment. For prolonged storage, an antimicrobial preservative should therefore be added to aqueous solutions. Aqueous solutions of hydroxyethyl cellulose may also be sterilized by autoclaving.

Hydroxyethyl cellulose powder should be stored in a well-closed container, in a cool, dry, place.

12. Incompatibilities

Hydroxyethyl cellulose is insoluble in most organic solvents.

Hydroxyethyl cellulose is incompatible with zein and partially compatible with the following water-soluble compounds: casein; gelatin; methylcellulose; polyvinyl alcohol and starch.

Hydroxyethyl cellulose can be used with a wide variety of water-soluble antimicrobial preservatives. However, sodium pentachlorophenate produces an immediate viscosity increase when added to hydroxyethyl cellulose solutions.

Hydroxyethyl cellulose has good tolerance for dissolved electrolytes although it may be salted out of solution when mixed with certain salt solutions, e.g. the following salt solutions will precipitate a 10% w/v solution of *Cellosize WP-09* and a 2% w/v solution of *Cellosize WP-4400*: sodium carbonate 50% and saturated solutions of aluminum sulfate; ammonium sulfate; chromic sulfate; disodium phosphate; magnesium sulfate; potassium ferrocyanide; sodium sulfate; sodium sulfite; sodium thiosulfate and zinc sulfate.

Natrosol is soluble in most 10% salt solutions, except sodium carbonate and sodium sulfate, and many 50% salt solutions except: aluminum sulfate; ammonium sulfate; diammonium phosphate; disodium phosphate; ferric chloride; magnesium sulfate; potassium ferrocyanide; sodium metaborate; sodium nitrate; sodium sulfite; trisodium phosphate and zinc sulfate. *Natrosol 150* is generally more tolerant of dissolved salts than *Natrosol 250*.

Hydroxyethyl cellulose is also incompatible with certain fluorescent dyes or optical brighteners, and certain quaternary disinfectants which will increase the viscosity of aqueous solutions.

13. Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with ethylene oxide, to produce a series of hydroxyethyl cellulose ethers.

The manner in which ethylene oxide is added to cellulose can be described by two terms: the degree of substitution (DS) and the molar substitution (MS). The degree of substitution designates the average number of hydroxyl positions on the anhydroglucose unit that have been reacted with ethylene oxide. Since each anhydroglucose unit of the cellulose molecule has three hydroxyl groups, the maximum value for DS is 3. Molar substitution is defined as the average number of ethylene oxide molecules that have reacted with each anhydroglucose unit. Once a hydroxyethyl group is attached to each unit, it can further react with additional groups in an end-to-end formation. This reaction can continue and, theoretically, there is no limit for molar substitution.

14. Safety

Hydroxyethyl cellulose is primarily used in ophthalmic and topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material.[6,7]

Acute and subacute oral toxicity studies, in rats, have shown no toxic effects attributable to hydroxyethyl cellulose consumption, the hydroxyethyl cellulose being neither absorbed nor hydrolyzed in the rat gastrointestinal tract. However, although used in oral pharmaceutical formulations hydroxyethyl cellulose has not been approved for direct use in food products, *see* Section 16.

Glyoxal-treated hydroxyethyl cellulose is not recommended for use in oral pharmaceutical formulations or topical preparations which may be used on mucous membranes. Hydroxyethyl cellulose is also not recommended for use in parenteral products.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxyethyl cellulose dust may be irritant to the eyes and therefore eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions. Hydroxyethyl cellulose is combustible.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral syrups and tablets, otic and topical preparations). Included in nonparenteral medicines licensed in the UK.

Hydroxyethyl cellulose is not currently approved for use in food products in Europe or the US although it is permitted for use in indirect applications such as packaging. This restriction is due to the high levels of ethylene glycol residues which are formed during the manufacturing process.

17. Pharmacopeias

Br, Eur, Fr, Ger, Gr, Hung, It, Neth, Port, Swiss and USPNF.

18. Related Substances

Ethylcellulose; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose; Methylcellulose.

19. Comments

The limited scope for the use of hydroxyethyl cellulose in foodstuffs is in stark contrast to its widespread application as an excipient in oral pharmaceutical formulations.

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22. Authors

USA: RJ Harwood, JL Johnson.

Hydroxypropyl Cellulose

1. Nonproprietary Names

BP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2. Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

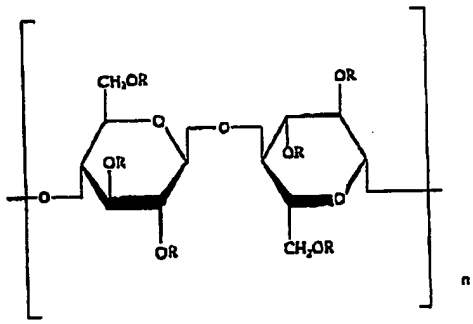
3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4. Empirical Formula Molecular Weight

The USPNF XVII describes hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or some other suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades which have different solution viscosities. Molecular weight ranges from 50 000–1 250 000, *see also* Section 10.

5. Structural Formula



Where R is H or $[-CH_2-CH(CH_3)-O]_mH$

6. Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating and extended release matrix former. Concentrations of between 2-6% w/w of hydroxypropyl cellulose may be used as a binder in either wet granulation or dry, direct compression tableting processes.[1-5] Concentrations of between 15-35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[6] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the hydroxypropyl cellulose viscosity and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Either aqueous solutions, containing hydroxypropyl cellulose along with some methylcellulose, or ethanolic solutions may be used.[7-9] Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant, *see* Section 18.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.[10-12]

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

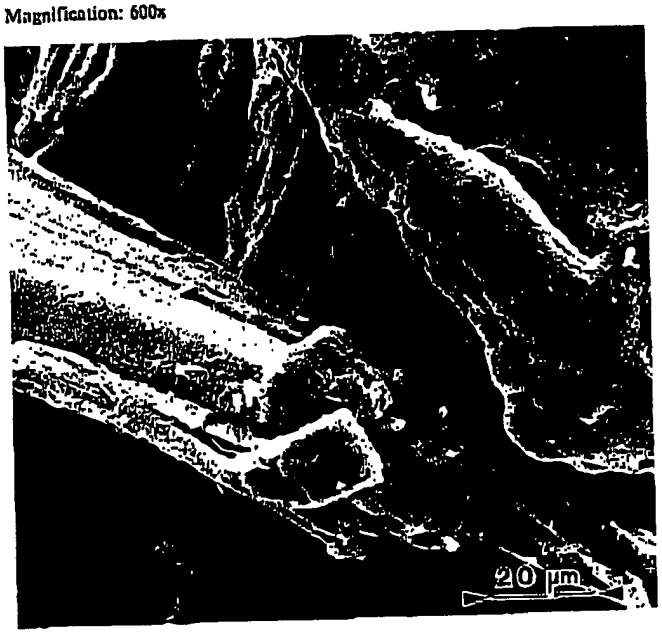
Use	Concentration (%)
Extended release matrix former	15-35
Tablet binder	2-6
Tablet film coating	5

8. Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. *See also* Sections 4 and 5.

SEM: 1
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 60x

SEM: 2
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 600x



9. Pharmacopeial Specifications

Test	PhEur 1992	USPNF XVII (Suppl 6)
Identification	+	+
Apparent viscosity	+	+
Appearance of solution	+	—
pH (1 in 100)	5.0-8.5	5.0-8.0
Loss on drying	≤ 7.0%	≤ 5.0%
Residue on ignition	—	≤ 0.2%
Sulfated ash	≤ 1.6%	—
Arsenic	—	≤ 3 ppm
Chlorides	≤ 0.5%	—
Lead	—	≤ 0.001%
Heavy metals	≤ 20 ppm	≤ 0.004%
Silica	≤ 0.6%	≤ 0.6%
Organic volatile impurities	—	+
Assay of hydroxypropoxy groups	—	≤ 80.5%

10. Typical Properties

Acidity/alkalinity:
pH = 5.0-8.5 for a 1% w/v aqueous solution.
Density (bulk): ≈ 0.5 g/cm^3
Interfacial tension: 12.5 mN/m for a 0.1% w/v aqueous solution versus mineral oil.
Melting point: softens at 130°C; chars at 260-275°C.
Moisture content: hydroxypropyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content, and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are: 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity. *See also* HPE Data.
Molecular weight:
for *Klucel EF* ≈ 80 000
for *Klucel LF* ≈ 95 000
for *Klucel JF* ≈ 140 000
for *Klucel GF* ≈ 370 000
for *Klucel MF* ≈ 850 000
for *Klucel HF* ≈ 1 150 000.
Particle size distribution: for *Klucel* (regular grind), 95% through a US #30 mesh (590 µm) and 99% through a US #20 mesh (840 µm); for *Klucel* (X-grind), 100% through a US #60 mesh (250 µm) and 80% through a US #100 mesh (149 µm).
Refractive index:
n_D^{20} = 1.3353 for a 2% w/v aqueous solution.
Solubility: soluble 1 in 10 parts dichloromethane, 1 in 2.5 parts ethanol, 1 in 2 parts methanol, 1 in 5 parts propan-2-ol, 1 in 5 parts propylene glycol and 1 in 2 parts water; practically insoluble in aliphatic hydrocarbons, aromatic hydrocarbons, carbon tetrachloride, petroleum distillates, glycerin and oils. Hydroxypropyl cellulose is freely soluble in water below 38°C forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40-45°C.
Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as: dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol; methanol; propan-2-ol (95%) and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids which are borderline solvents, such as: acetone; butyl acetate; cyclohexanol; dichloromethane; lactic acid; methylacetate; methylethyl ketone; propan-2-ol (99%) and *tert*-butanol. The higher viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5-15%) of a cosolvent. For example, dichloromethane is a borderline solvent for *Klucel HF* and solutions have a granular texture, but by adding 10% methanol a smooth solution may be produced.
Hydroxypropyl cellulose is compatible with a number of high molecular weight, high boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are: acetylated monoglycerides; glycerides; pine oil; polyethylene glycol and polypropylene glycol.
Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.
Surface tension: *see* Table I.

Table I: Surface tension (mN/m) of aqueous solutions of *Nisso HPC* (Nippon Soda Co Ltd) at 20°C.

Grade	Surface tension at 20°C (mN/m) Concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Viscosity (dynamic): a wide range of viscosity types are commercially available, *see* Table II and HPE Data. Solutions should be prepared by gradually adding the hydroxypropyl

cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. *See also* Section 11 for information on solution stability.

Table II: Viscosity of aqueous solutions of *Klucel* (Aqualon) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions Concentration			
	1%	2%	5%	10%
Klucel HF	1500-3000	—	—	—
Klucel MF	—	4000-6500	—	—
Klucel GF	—	150-400	—	—
Klucel JF	—	—	150-400	—
Klucel LF	—	—	75-150	—
Klucel EF	—	—	—	200-600

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content			
Type LH-21[a]	MC-7	14	3.81% [(a)]
Klucel HF	MC-7	14	4.27% [(b)]
Klucel MF	MC-7	14	1.52% [(b)]
Klucel GF	MC-7	14	1.67% [(b)]
Klucel JF	MC-7	14	1.44% [(b)]
Klucel LF	MC-7	14	2.21% [(b)]
Klucel EF	MC-7	14	0.59% [(b)]
Klucel	EMC-1	15	*See* Fig. 1. [(b)]
Type LH-11[a]	SDI-1	14	*See* Fig. 2. [(a)]
Klucel HF	SDI-1	14	*See* Fig. 2. [(b)]
Klucel MF	SDI-1	14	*See* Fig. 2. [(b)]
Klucel EF	SDI-1	14	*See* Fig. 3. [(b)]
Klucel GF	SDI-1	14	*See* Fig. 3. [(b)]
Klucel JF	SDI-1	14	*See* Fig. 3. [(b)]
Klucel LF	SDI-1	14	*See* Fig. 3. [(b)]
Particle friability	PF-1	36	0.125% [(c)]
Solubility [(c)]			
Ethanol (95%) at 25°C	SOL-7	32	0.14 mg/mL
Ethanol (95%) at 37°C	SOL-7	32	0.24 mg/mL
Hexane at 25°C	SOL-7	32	1.0 mg/mL
Hexane at 37°C	SOL-7	32	1.0 mg/mL
Propylene glycol at 25°C	SOL-7	32	1.0 mg/mL
Propylene glycol at 37°C	SOL-7	32	1.0 mg/mL
Water at 25°C	SOL-7	32	500 mg/mL
Water at 37°C	SOL-7	32	500 mg/mL
Viscosity [(b)]			
Klucel EF (10% w/v)	VIS-1	6	410-740 mPa s
Klucel GF (2% w/v)	VIS-1	6	360-615 mPa s
Klucel GF (3% w/v)	VIS-1	6	1350-1625 mPa s
Klucel HF (1% w/v)	VIS-1	6	1800-3250 mPa s
Klucel HF (2% w/v)	VIS-1	6	2325-3300 mPa s

Supplier: a. Biddle Sawyer Corporation; b. Aqualon; c. Shin-Etsu Chemical Co Ltd.

[a] Note that *Type LH-11* and *LH-21* are low-substituted grades of hydroxypropyl cellulose, *see also* Section 18.

11 Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable between pH 6.0-8.0 with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, which causes chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration. At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur due to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to gradually decrease until the viscosity drops

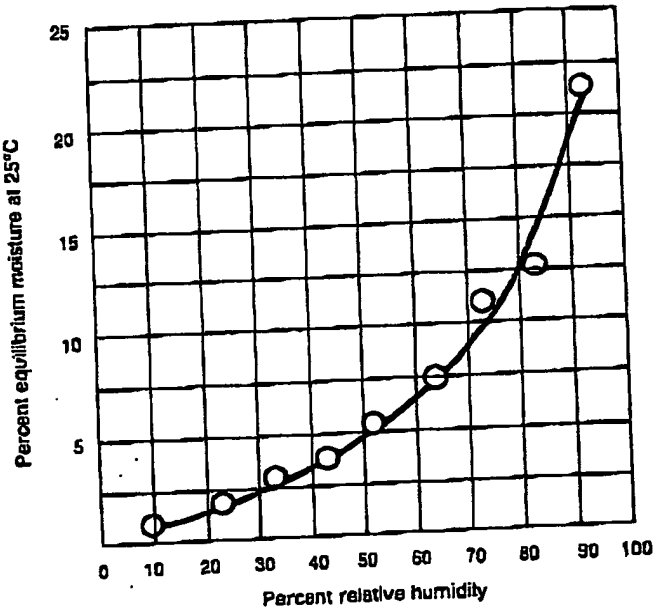


Fig. 1: Equilibrium moisture content of hydroxypropyl cellulose (*Klucel*).

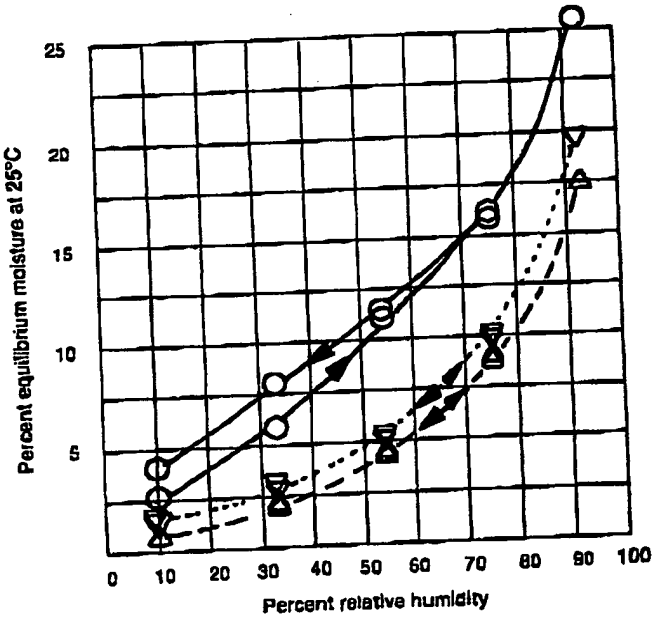


Fig. 2: Equilibrium moisture content of various grades of hydroxypropyl cellulose.
○ *Type LH-11* (Biddle Sawyer Corporation, Lot #8069).
△ *Klucel HF* (Aqualon, Lot #1061).
▽ *Klucel MF* (Aqualon, Lot #1294).
Note that *Type LH-11* is a low-substituted grade of hydroxypropyl cellulose.

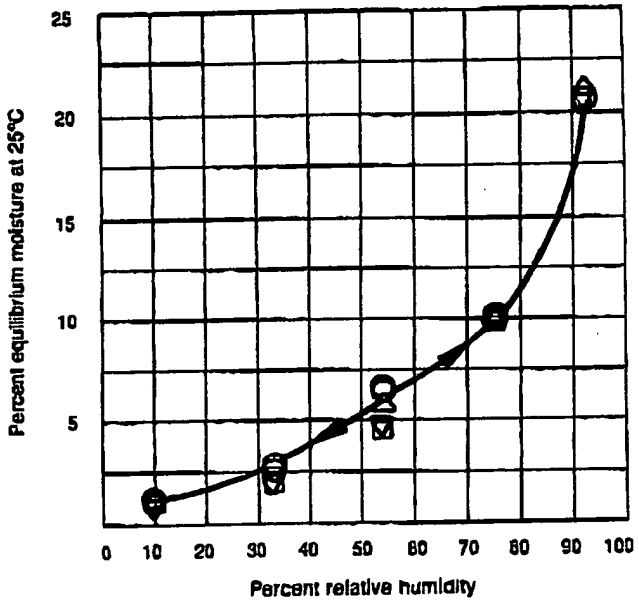


Fig. 3: Equilibrium moisture content of various grades of hydroxypropyl cellulose.
○ *Klucel GF* (Aqualon, Lot #4996).
△ *Klucel JF* (Aqualon, Lot #4753).
▽ *Klucel LF* (Aqualon, Lot #4965).
□ *Klucel EF* (Aqualon, Lot #1223).

suddenly at about 45°C due to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.[9] However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may thus occur. Certain enzymes, produced by microbial action, will degrade hydroxypropyl cellulose in solution.[13] For prolonged storage, an antimicrobial preservative should therefore be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore slightly decrease in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions thus have optimum stability when the pH is maintained between pH 6.0-8.0 and the solution is protected from light, heat and the action of microorganisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration, *see* Table III; hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials. The balance of the hydrophilic-lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system, *see* Table IV.

Table III: Compatibility of hydroxypropyl cellulose (*Nisso HPC*) with inorganic salts in aqueous solutions.

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferrocyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

S: completely soluble T: turbid white I: insoluble

Table IV: Variation in precipitation temperature of hydroxypropyl cellulose (*Klucel H*) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% *Klucel H*	41
1% *Klucel H* + 1.0% NaCl	38
1% *Klucel H* + 5.0% NaCl	30
0.5% *Klucel H* + 10% Sucrose	41
0.5% *Klucel H* + 30% Sucrose	32
0.5% *Klucel H* + 40% Sucrose	20
0.5% *Klucel H* + 50% Sucrose	7

13. Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This results in the formation of side chains containing more than one mole of combined propylene oxide.

14. Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also extensively used in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.[14] However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare but have included a report, in a single patient, of allergic contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.[15] The WHO has not specified an acceptable daily intake for hydroxypropyl cellulose since the levels consumed were not considered to represent a hazard to health.[16] Excessive consumption of hydroxypropyl cellulose may however have a laxative effect.

LD_{50} (mouse, IP): > 25 g/kg[17]
LD_{50} (mouse, IV): > 0.5 g/kg
LD_{50} (mouse, oral): > 5 g/kg
LD_{50} (rat, IP): > 25 g/kg
LD_{50} (rat, IV): 0.25 g/kg
LD_{50} (rat, oral): 10.2 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Eur, Fr, Ger, Hung, It, Jpn, Neth, Port, Swiss and USPNF.

18. Related Substances

Hydroxyethyl Cellulose; Hydroxypropyl Methylcellulose; low-substituted hydroxypropyl cellulose.

Low-substituted hydroxypropyl cellulose:

CAS number: [78214-41-2]
Synonyms: cellulose, 2-hydroxypropyl ether (low-substituted); *L-HPC*.
Pharmacopeias: Jpn and USPNF.
Angle of repose:
49° for *L-HPC Type LH-11*;
45° for *L-HPC Type LH-21*.
Density (bulk):
0.34 g/cm³ for *L-HPC Type LH-11*;
0.40 g/cm³ for *L-HPC Type LH-21*.
Density (tapped):
0.57 g/cm³ for *L-HPC Type LH-11*;
0.65 g/cm³ for *L-HPC Type LH-21*.
Moisture content: ≤ 5.0% w/w
Particle size distribution: average particle size for *L-HPC Type LH-11* is 50.6 μm; for *L-HPC Type LH-21* it is 41.7 μm.[18]
Solubility: insoluble in water but swells.
Specific gravity: 1.46
Specific surface area:[18]
L-HPC Type LH-11 = 2.70 m²/g;
L-HPC Type LH-21 = 3.20 m²/g;
L-HPC Type LH-31 = 5.24 m²/g;
L-HPC Type LH-41 = 31.60 m²/g.
Safety: LD_{50} (rat, oral): > 15 g/kg[17]
Comments: a low-substituted hydroxypropyl cellulose containing 5-16% of hydroxypropoxy groups. Used as a sustained release tablet matrix former and as a tablet disintegrant.[18,19]

19. Comments

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

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Hydroxypropyl Methylcellulose

1. Nonproprietary Names

BP: Hypromellose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

2. Synonyms

Cellulose, hydroxypropyl methyl ether; *Culminal MHPC*; E464; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*.

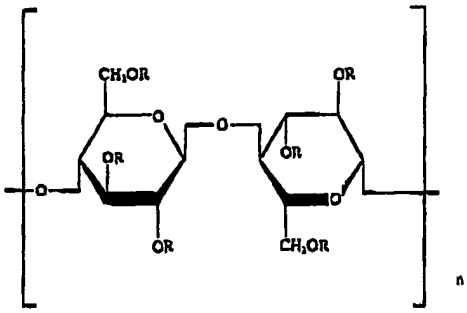
3. Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether
[9004-65-3]

4. Empirical Formula Molecular Weight

The PhEur 1992 describes hydroxypropyl methylcellulose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hydroxypropyl methylcellulose defined in the USP XXII specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000.

5. Structural Formula



Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$.

6. Functional Category

Coating agent; film-former; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder,[1] in film-coating[2-7] and as an extended release tablet matrix.[8-12] Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix.

Depending upon the viscosity grade, concentrations between 2-10% w/w are used as film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hydroxypropyl methylcellulose is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8. Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

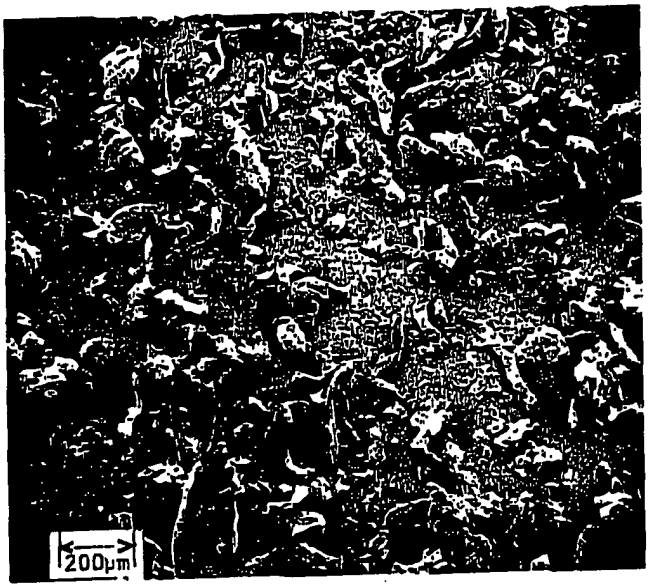
9. Pharmacopeial Specifications

Test	PhEur 1992	USP XXII (Suppl 2)
Identification	+	+
Appearance of solution	+	—
pH (1% w/w solution)	5.5-8.0	—
Apparent viscosity	+	+
Loss on drying	⩽ 10.0%	⩽ 5.0%
Residue on ignition		
for viscosity grade > 50 mPa s	—	⩽ 1.5%
for viscosity grade ⩽ 50 mPa s	—	⩽ 3.0%
for type 1828 of all viscosities	—	⩽ 5.0%
Sulfated ash	⩽ 1.0%	—
Arsenic	—	⩽ 3 ppm
Chlorides	⩽ 0.5%	—
Heavy metals	⩽ 20 ppm	⩽ 0.001%
Methoxy content		
Type 1828	—	16.5-20.0%
Type 2208	—	19.0-24.0%
Type 2906	—	27.0-30.0%
Type 2910	—	28.0-30.0%
Hydroxypropoxy content		
Type 1828	—	23.0-32.0%
Type 2208	—	4.0-12.0%
Type 2906	—	4.0-7.5%
Type 2910	—	7.0-12.0%

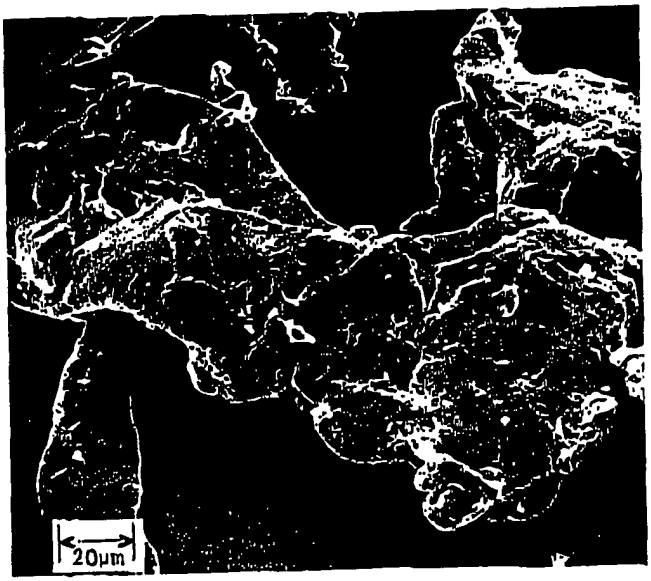
10. Typical Properties

Acidity/alkalinity:
pH = 5.5-8.0 for a 1% w/w aqueous solution.

SEM: 1
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Shin-Etsu Chemical Co Ltd
Lot No.: 83214
Magnification: 60x
Voltage: 10kV



SEM: 2
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Shin-Etsu Chemical Co Ltd
Lot No.: 83214
Magnification: 600x
Voltage: 10kV



Ash: 1.5-3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (tapped): 0.50-0.70 g/cm^3 for *Pharmacoat*.
Melting point: browns at 190-200°C; chars at 225-230°C. G transition temperature is 170-180°C.
Moisture content: hydroxypropyl methylcellulose abs moisture from the atmosphere, the amount of water absor depending upon the initial moisture content and temperature and relative humidity of the surrounding *See also* HPE Data.
Solubility: soluble in cold water, forming a viscous colloi solution; practically insoluble in chloroform, ethanol (95 and ether, but soluble in mixtures of ethanol and dichl omethane, and mixtures of methanol and dichlorometha Certain grades of hydroxypropyl methylcellulose are solubl aqueous acetone solutions, mixtures of dichloromethane propan-2-ol, and other organic solvents. *See also* Section 1
Specific gravity: 1.26
Viscosity (dynamic): a wide range of viscosity types commercially available. Aqueous solutions are most co monly prepared although hydroxypropyl methylcellulose m also be dissolved in aqueous alcohols such as ethanol a propan-2-ol provided the alcohol content is less than 50% w/ Dichloromethane and ethanol mixtures may also be used prepare viscous hydroxypropyl methylcellulose solutio Solutions prepared using organic solvents tend to be mo viscous; increasing concentration also produces more visco solutions, *see* Table I.
To prepare an aqueous solution, it is recommended th hydroxypropyl methylcellulose is dispersed and thorougl hydrated in about 20-30% of the required amount of wat The water should be vigorously stirred and heated to 80-90 then the remaining hydroxypropyl methylcellulose add Cold water should then be added to produce the requir volume.
When a water-miscible organic solvent such as ethanol, glyc or mixtures of ethanol and dichloromethane is used, hydroxypropyl methylcellulose should first be dispersed ir the organic solvent, at a ratio of 5-8 parts of solvent to 1 p of hydroxypropyl methylcellulose. Cold water is then added produce the required volume.

Table I: Dynamic viscosity (mPa s) of *Pharmacoat 603* (Shin-Etsu Chemical Co Ltd) solutions in various solvents at 20°C.

Solvent	Viscosity (mPa s) at 20°C Concentration (% w/w)			
	2	6	10	14
Dichloromethane: ethanol (50:50)	4	28	150	580
Ethanol: water (50:50)	8	32	120	350
Water	3	15	45	100

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content	MC-20	15	2.10% [a]
Moisture content	MC-20	15	3.10% [b]
Moisture content	EMC-1	15	*See* Fig. 1.

Supplier: a. Dow Chemical Company; b. Aqualon.

11. Stability and Storage Conditions

Hydroxypropyl methylcellulose powder is a stable mate although it is hygroscopic after drying.

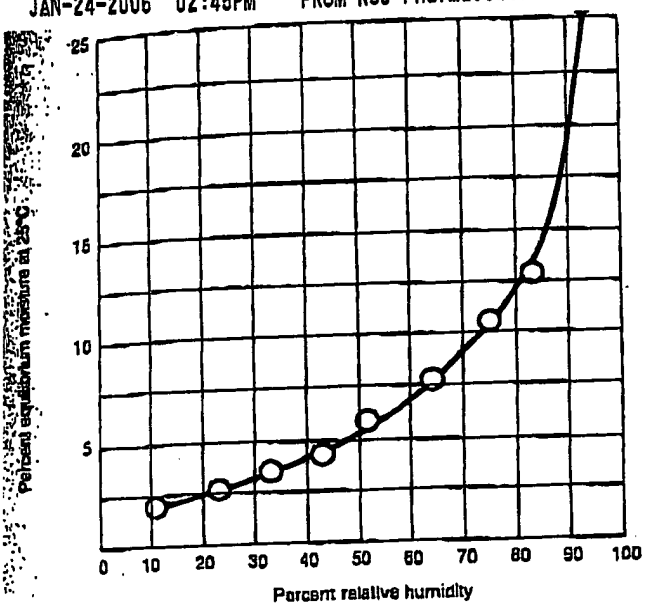


Fig. 1: Equilibrium moisture content of hydroxypropyl methylcellulose, *Methocel E15* (Dow Chemical Company, Lot No.: QP0502-801-E).

Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solutions. Hydroxypropyl methylcellulose undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90°C, depending upon the grade of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.[13] However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. When used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used for this purpose. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hydroxypropyl methylcellulose powder should be stored in a well-closed container, in a cool, dry, place.

12. Incompatibilities

Hydroxypropyl methylcellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxypropyl methylcellulose will not complex with metallic salts and ionic organics to form insoluble precipitates.

13. Method of Manufacture

A purified form of cellulose, obtained from cotton waste or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methylhydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14. Safety

Hydroxypropyl methylcellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.[14] The WHO has not specified an acceptable daily intake for hydroxypropyl methylcellulose since the levels consumed were not considered to represent a hazard to health.[15]

LD_{50} (mouse, IP): 5 g/kg[16]

LD_{50} (rat, IP): 5.2 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl methylcellulose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions. Hydroxypropyl methylcellulose is combustible.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules, suspensions, syrups and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Eur, Fr, Gr, It, Jpn, Neth, Port, Swiss and US.

18. Related Substances

Hydroxyethyl Cellulose; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose Phthalate.

19. Comments

Powdered or granular, surface-treated grades of hydroxypropyl methylcellulose are also available which are dispersible in cold water. The dissolution rate of these materials can be controlled by a shift in pH and they are thus useful for slow-release or enteric coated formulations.

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22. Authors

USA: RJ Harwood, JL Johnson.